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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,477	10/04/2001	Attila T. Lorincz	2629-4005US4	2780

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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,477	LORINCZ ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *8-22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL REJECTION

1. This action is responsive to the Amendment and Response filed 23 November 2005, to the complying Amendments to the Specification filed 14 March 2006. Claim 8 has been amended, and claims 8-22 are pending and under consideration. Applicants' amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

3. With regard to the recitation "25 µl of Detection Reagent 1" in the Amendments to the Specification filed 14 March 2006, it is noted that this recitation was present in the originally filed specification and that, as the Amendments to the Specification of 23 November 2005 were not entered (due to non-compliance; see the Communication mailed 16 February 2006), this recitation does not in fact constitute an amendment to the specification and does not introduce new matter.

4. In view of Applicants' amendments to the specification deleting the recitation "to calibrators and cellular RNA" at page 23, the objection under 35 U.S.C. 132 set forth in the prior Office action of 26 August 2005 is withdrawn.

THE FOLLOWING ARE NEW GROUNDS OF OBJECTION NECESSITATED BY APPLICANTS' AMENDMENTS TO THE SPECIFICATION:

5. The amendment filed 14 March 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: on page 23, at line 14, the insertion of the language "isolated and." The specification has been amended so as to recite that "total RNA was isolated and purified" whereas it previously recited "total RNA was purified." The insertion of the language "isolated and" indicates an additional action/step taken in RNA processing for which basis was not provided in the originally filed specification, and therefore constitutes the addition of new matter.

It is noted that the instant amendment was introduced previously (see the amendment to the specification filed 13 June 2003) and was objected to on the same grounds set forth above in the Final Action mailed 19 April 2004. Subsequently, Applicant amended the specification so as to delete the "isolated and" recitation (see the amendment of 18 October 2004).

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, first paragraph

6. Claims 8-12 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons set forth in the Office action of August 26, 2005.

It is again noted that the Declaration under 35 USC 1.132 filed May 18, 2005 was found to be sufficient to overcome the rejection of claims 8-12 in part, as discussed in the prior Office action of August 26, 2005. Specifically, the Declaration establishes

enablement of the claims to the extent that they are drawn to diagnosis of HPV16-induced cancer and stages thereof by detecting in patients the ratios encompassed by the claims.

The response traverses the rejection on a variety of grounds. Applicants' arguments have been thoroughly considered but are not persuasive, for the reasons discussed below.

First, it is noted that the examiner agrees that enablement "is determined with respect to the state of knowledge in the field and differences in the predictability of the science at issue." In reaching the determination that the instant claims are only partially enabled, the examiner has considered the state of knowledge in the field of HPV-induced disease diagnosis, and the extent to which one may predict results in patients based on findings in cultured cells, as well as the extent to which expression patterns and ratios observed with one type of HPV might correlate with patterns and ratios obtained with other HPV types (or subsets of HPV types). Applicant is referred to the Office actions of April 19, 2004 and August 26, 2005. With regard to *Invitrogen v. Clontech* (Slip Opinion 04-1039, -1040, November 18, 2005), it is noted that the instant claims are not drawn to a product that may be prepared using a method disclosed in the specification (and which are thus enabled because the specification teaches at least one method that may be used to prepare the claimed product, as was the case in *Invitrogen*). Rather, in the instant case, the claims as written encompass methods of diagnosing a variety of different HPV types, while the specification (when considered in combination with the above-referenced Declaration) only enables the diagnosis of one

HPV type (HPV 16). As applicant has not in fact shown any way to practice methods encompassed by the claims with regard to HPV types other than HPV 16 without undue experimentation, the enablement of the claims is limited to HPV 16.

With regard to the Lorincz Declaration of May 18, 2005, it is again noted that the prior art references relied upon by Lorincz are silent with regard to correlations between HPV 16 gene expression ratios and those of other "high risk" HPV types. The fact that multiple HPV types are associated with cervical cancer and that multiple HPV types have "similar expression patterns" would not lead a skilled artisan to conclude that the particular ratios of the instant claims could be relied upon in the diagnosis of disease caused by HPV types other than HPV 16. Enablement of the instant claims does not require a mere similarity in gene expression patterns – a correlation in ratios would require analogous changes in expression of multiple, different groups of genes. While one could clearly conduct further experiments aimed at determining whether the ratios of the claims are valid with regard to other HPV types, the outcome of such experimentation is completely unpredictable, and it is unknown as to whether any quantity of experimentation would result in a conclusion that the claims are enabled for diagnosis with regard to any HPV type other than HPV 16. Applicants' assertions that "the teachings of the instant application can be readily converted to use in any HPV strain," that "One skilled in the art can readily adopt this method for an HPV strain without undue experimentation," etc., are simply not supported by the teachings of the art, the specification, and/or the Declaration.

Further (as discussed in the Office action of August 26, 2005), Applicant's Declaration does not establish a correlation between transcript ratios in HeLa cells and patients with a particular stage of HPV 18 induced disease, or between transcript ratios in LKP31 and/or A31 cells and patients with particular stages of HPV 31-induced disease. With further regard to HPV 18, the Declaration does not indicate with which of the three types/stages of disease disclosed in the specification the HeLa cell model is believed to correlate, or provide evidence of such a correlation. Thus, with regard to the ratio of 9.5 detected in HeLa cells, it is unpredictable whether: a) such a ratio might ever be detected in a patient, b) whether such a ratio in a patient would indicate a correlation with the disease stage present in the HeLa cells employed by the Declarant, and c) what disease state such a ratio in a patient would indicate. Similarly, with further regard to HPV 31, the Declaration does not indicate with which of the three types/stages of disease disclosed in the specification the LKP31 and A31 cell models are believed to correlate. While Declarant does indicate that LKP31 is "assumed to represent a cell line that is closer to cancer" due to its higher HPV 31 copy number, the Declaration does not indicate whether one or both of these cell lines represents cancer, a pre-malignancy, etc. It is further noted that these two cell lines are disclosed to be structurally different from the HPV 16 models of the specification (see the discussion on page 8 of the Office action of August 26, 2005). It is not apparent how or whether the LKP31 and A31 models relate either to different stages of HPV 31 induced disease, or to the HPV 16 models of the specification. Thus, with regard to the ratios of 11.7 for LKP31 cells and 8.4 for A31 cells, it is unpredictable whether: a) such ratios might ever be detected in a

patient, b) whether such a ratio in a patient would indicate a correlation with disease stages present in the LKP31 and A31 cells employed by the Declarant, and c) what disease states such ratios in a patient would indicate. (With regard to Applicants' statements at page 11 of the Response, it is also noted that Applicants' references to "Table 3 of the instant specification" and "Table 7 of the instant specification" in fact refer to Tables present in the Declaration; no such Tables presenting data obtained with HPV 18 and/or HPV 31 are present in the originally filed specification).

With regard to Applicants' statement that the "cell lines that are used in these experiments represent *in vivo* conditions," it is noted that this statement is merely an assertion; Applicants have not provided evidence that, e.g., gene expression levels measured in the cell lines in which HPV 18 and HPV 31 were assayed correlate with levels measured in patients at a particular disease stage, nor have Applicants' provided any references that support such an assertion. With regard to *Cross v. Iizuka* (753 F.2d 1040, 1050, 224 USPQ 739 (Fed.Cir. 1985) and *Nelson v. Bowler* (626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980), it is noted that the examiner has not rejected the instant claims for a lack of utility, but rather for a lack of enablement. With regard to the *in vitro* assay at issue in *Nelson v. Bowler*, the assay was one that both parties acknowledged as simulating *in vivo* activity (and another, *in vivo*, assay was also relied upon in establishing utility); in the instant case, no such correlation has been established. In *Cross v. Iizuka*, the court found that an *in vitro* utility for a pharmacological agent was sufficient to meet the utility requirement, and further relied upon the fact that "the disclosed *in vitro* utility is supplemented by the similar *in vitro* and *in vivo*

pharmacological activity of structurally similar compounds, i.e., the parent....compounds." In neither *Nelson v. Bowler* nor *Cross v. Iizuka* did the court conclude that *in vitro* findings alone were sufficient to meet the utility requirement (or to enable *in vivo* treatment/diagnosis); rather, additional evidence of a correlation with *in vivo* findings was also relied upon. The facts of the instant case are not analogous to those of *Nelson v. Bowler* or *Cross v. Iizuka,* and thus these arguments are not persuasive.

Applicants' arguments are not persuasive for the reasons given above. Accordingly, this rejection is maintained.

7. Claims 13-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons set forth in the Office action of August 26, 2005.

The response traverses the rejection on the same grounds set forth in paragraph 6, above. The response to those arguments applies equally herein. Accordingly, this rejection is maintained.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Primary Examiner
Art Unit 1634

5/30/06